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ОРИГИНАЛЬНАЯ СТАТЬЯ

TRACE ELEMENT METABOLIC IMAGING OF THE MAJOR UNIPOLAR CLINICAL DEPRESSION – SILVER IN THE HAIR AND BLOOD

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KEY WORDS: Major unipolar clinical depression, trace element metabolic imaging, hair silver, blood silver

SUMMARY. The metabolism of silver (Ag) is briefly reviewed. Silver is a non-essential trace element generally considered to be non-toxic under the usual environmental levels of exposure, but when excessive, a clinical picture of silver toxicity (argyria) may develop. Silver is strong superficial bactericidal agent in men, but its biological role is poorly understood. In this study we analyzed silver in the hair and blood of 48 subjects with major unipolar clinical depression (15 men and 33 women) and 48 healthy control subjects (23 men and 25 women) age 20 –92 years in the randomized double-blind prospective clinical-epidemiological investigation on multielement profile of depression. All the 96 hair samples were well within the detection limits for ICP MS analysis, whereas, silver in the blood was detected in 45 subjects since 15 were lost in preparation and 36 were below the detection limits. We identified a strong depression associated cluster for subjects having simultaneously silver values above 0.033 μg/g for the hair and 0.0018 μg/g for the blood, respectively. The diagnosis of major unipolar clinical depression is almost certain when both silver in the hair and in the blood are increased above the stated values. The antagonism of silver with copper and selenium is discussed.

Introduction

Depression is the most frequent mental impairment/illness in the world (Licino, Wong, 2005) but, however, there are no data available to our knowledge, about the possible role of silver in depression

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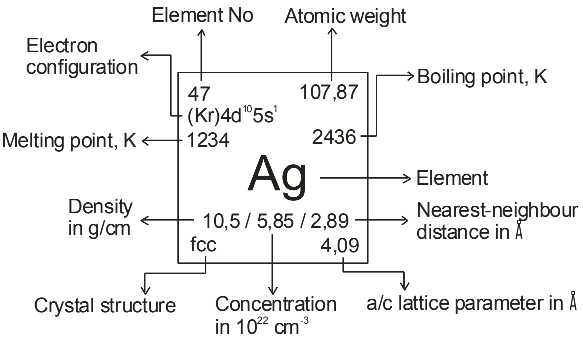
Silver is a non-essential trace element of low toxicity for men and of high germ killing potential (Emsley, 2001); it also has numerous industrial application (Harbison, 1998) and what won't be discussed here further. Silver germ killing potential was known since the ancient times when Persian invasion forces used silver to keep the water fresh, an efficient rival to the today's drinking water chlorination practice (Smith, Carson, 1977). It has been used in the Arabic and ajurvedic medicine due to the presumed magic properties, and was known as a moon symbol in medieval alchemy (Doherty, 2004). Since the last half of the 19th century, silver was used in the eye drops to prevent the newborn blindness of sexually transmitted diseases (gonorrhea) (Grasshoff, King, 1990). Soon it was found that silver is a potent germ killer in the wounds of the burned patients (Klasen, 2000a,b), and ever since numerous silver nitrate ointments with sulphadiazine were developed, (like Dermasine, Lek, Ljubljana, Slovenia), as topical bactericidal agent for the burn wounds (Harrison, 1979; Stern, 1989). Today, the whole nano-technology industry of the silver coated indwelling blood and urine catheters and other prosthetic devices has been developed so that, e.g., urinary catheters may stay in place for up to three weeks without developing infection (Multanen et al., 2000). The reason for this high germ killing potential of silver associated with the low toxicity for humans is still not understood (Hollinger, 1996). Apparently, silver has an extremely high oxygen biding capacity and what may affect the bacterial metabolic pathways in a different manner than in the higher developed mammals (Klueh et al., 2000). Moreover, like zinc, copper, cadmium and some other metals (Momčilović, Reeves, 1997), silver is a strong methallothionein inductor and what may substantially decrease its own toxicity (Winge et al., 1975).

Silver is considered to be the naturally occurring food contaminant (Reilly, 2002), and it's daily intake in the average European diet is very low, about 20 μg per



Vignette 1. Silver structure – Modern view. [to be inserted in the indented space at the beginning of the Introduction].

day (Tipton et al., 1963; Hamilton et al., 1972/1973); but it can be much higher in the Moslem countries in Asia and Africa (Tipton et al., 1965). Apparently, silver is not absorbed via the intact skin (Guy et al., 1999), and gastrointestinal absorption is generally considered to be very low, most likely around 1% (Ratte, 1999). Moreover, the kinetics of non-toxic doses of silver on whole body retention, tissue distribution, and excretion is poorly studied (Furchner et al., 1968). Results of Tipton et al. (1963) seems to indicate silver affinity for the fat tissues of the body. There are some suggestion that most of silver accumulates in the liver, like did the copper from the same copper – silver – gold group in the Periodic system (Momčilović, 2007). Silver tends to accumulate in the papillary dermis and along the dermo/epidermal junction, particularly around sweat glands (Wan et al., 1991; Lansdown et al., 1997); this is also the region where a lot of immunological CD4 and CD8 action is taking place in both health and disease (Roith et al., 1985). Silver also has a high affinity for the nervous tissue cells and has been used for histological staining of the brain since the time of Raymon y Cajal (Rungby, 1990; Newman, Jasani, 1998). Indeed, prolonged exposure to silver may change the nucleic acid level in the rat brain (Kharchenko et al., 1973). Silver is poorly excreted in the urine; fecal excretion of silver predominates over urinary excretion because of biliary excretion of silver into the intestine by the liver (Harbison,1998).

Cases of silver over-exposure are rare and well known and a clinical condition associated with the excessive silver intake is known as argyria (Petering, 1976; Skalny, 1999). Inhalation of 10 mg/m^3 of soluble silver for long periods and ingestion of 1 to 5 g of soluble silver may result in generalized argyria. Generalized argyria is characterized by the gray slate color of the skin (and sclera) particularly at the sun-exposed areas (Pariser, 1968; Zatouroff, 1976; Lee, Lee, 1994). The color is the result of silver sulfide as well as metallic silver deposition and ultimately is produced by photoactivated reduction. The localized argyria is common in jewelry workers where the skin discoloration often resembles small dermal nevi (Buckley, 1963; Flora et al., 1990). The condition is considered not to be harmful, but the deposited silver would remain in the position like the permanent tattoo (Sarsfield et al., 1992). A rare case of skin allergy to the very high skin exposure to silver fulminate was also described in a not so distant past (White, Rycroft, 1982). More often the lichenoid response of the oral mucosa was reported to the silver containing oral amalgam (Lind et al., 1986; Laine et al., 1997).

Criteria for establishing argyrosis are not clearly set so that a occupationally exposed silver worker with blood levels of silver of 49 μg/L was proclaimed not to have signs of argyria, whereas the worker from the same plant with blood levels of 74 μg/L was proclaimed to have argyrosis albeit there were no other health effects observed (Williams, Gardner, 1995). Silver toxicity has been demonstrated in vitro at serum levels higher than 0.3 mg/L when significant reduction in cell proliferation was observed (Wataha et al., 2000). Mucosal irritation, cough, and chest tightness were reported for the workers exposed to inhalation of high silver nitrates with no signs of nephrotoxic effects (Roseman et al., 1987). Inhalation is considered to be the primary route for high silver ingestion and current industrial hygiene standards allow for exposure of 0.01 mg/m^3 (NIOSH 1994). The ACGIH (1996) has set the threshold limit value (TLV) for the metal silver at 0.1 mg/m^3 and the TLV for soluble silver at 0.01 mg/m^3. It should be noted that respiratory symptoms of silver exposure, in fact, may have come from cadmium contamination of the melted ore (Vance, 1960).

In the previous paper (Momčilović et al., 2006a), we provided the general introduction to the rationale and design of the multielement profile analysis of hair and blood for the metabolic imaging of the major unipolar clinical depression. The aim of this paper is to show our results on the metabolism of silver in the depressed and control subjects as a first step towards the elucidation of possible element clustering and interaction in this mental illness.

Subjects and methods

In this prospective, randomized, double blind, clinical-epidemiological study of depression, the multielement profile in the hair and whole blood was analyzed in 96 subjects over the period of three years.

There were 48 subjects (15 men and 33 women) who were clinically diagnosed to have major clinical unipolar depression (APA, 1994); another 48 subjects (23 men and 25 women) with no apparent health problems served as a control. Subjects were selected, and hair and blood samples were collected, coded, washed, digested, and finally analyzed for silver by the inductively coupled plasma mass spectrometry (ICP-MS) as described

Table 1. Number of hair and blood samples analyzed for silver in depressed and control subjects.

	Hair (n = 96)		Blood (n = 45)	
	Men	Women	Men	Women
Control	23	25	12	10
Depression	15	33	6	17

previously (Momčilović et al., 2006a).

Silver was detected in the hair of all the 96 subjects, whereas silver in the whole blood was below the detection limits of ICP-MS for 36 subjects, and for 15 more subjects the whole blood samples were lost in preparation (Table 1). ANO Center for Biotic Medicine, Moscow, reference values for silver (Ag μg/g) are set at 0.000 – 0.800 and 0.000 – 0.005 for hair and whole blood for both women and men, respectively (Momčilović et al., 2006a).

The results were analyzed by the analysis of variance (ANOVA), chi-square test, and regression analysis (Momčilović et al., 2006a).

This study was planned and conducted in the full compliance with ethical principles of the Helsinki Declaration and local Laws and regulations (Derenzo and Moss, 2006).

Results

The code number of every subject which was used to double blind the samples, and the entire data set of silver in blood and hair are shown in the Appendices 1 and 2, respectively. There were no difference between the control and depressed subjects by ANOVA; most probably due to the few very high silver outliers in both the hair and whole blood (Fig. 1 and Fig. 2). Evidently, silver has about two orders of magnitude higher affinity for the hair deposition than for the whole blood retention.

When the silver concentration in the hair and blood is shown such that the values were arranged in sequence from the lowest to the highest (rank sequence) for control and depressed subjects separately, the visual examination of the plots revealed two apparently distinct curves. Both curves may be fitted to the quadratic equation (data not shown), but that fitting was considered to be questionable since there were only few points available for the high silver in the whole blood and hair concentration.

Next, we studied the early part of the rank sequence for both hair (Fig. 3) and whole blood (Fig. 4) for control and depressed subjects, respectively (see the inserts to the Fig. 3 and Fig. 4). This part of the rank sequence curve appears to be linear and can be subjected to the regression analysis; the slope for the depressed subjects was higher than that for the controls ($P < 0.05$) (Table 2). Indicating that there were more silver accumulated in the hair of depressed than in the control subjects for that linear part of the curve. However, albeit there was a tendency towards the steeper slope for the depressed subjects, the difference in the slope of the regression lines for silver content of the control and depressed subjects was not significant; most likely due to the relatively small number of the samples available.

Then, we made a cross-plot for the 45 available subjects where we have analyzed silver in both the hair and whole blood (Fig. 5). The CBM reference values for silver in the hair and blood appears to be too "liberal" (wide) and, indeed, there were only one high hair silver value and six high silver values in the whole blood. Visual examination of the plots suggested for the more strict silver reference values to be established, i.e., 0.033 and 0.0018 μg/g for the hair and whole blood, respectively (IMI). That allows us to identify a cluster of eight depressed women and two men with both high hair and whole blood silver, respectively (Fig. 5, Table 3).

The only "intruder" into this high depression incidence cluster was a male plumber (No. 050) from the control group who appears to be exposed to variety of metals in his trade. His medical status was rigorously re-evaluated; he admitted some "light" alcohol abuse, and showed some mild liver function impairment as reflected by the increased SGOT and SGPT. This case also demonstrated the importance of tracking the fate of every single subject in a randomized, double blind clinical-epidemiological investigation such as provided by the Code matrix (Appendix 1) and combined with the analogous topological maps with the actual trace element sample concentration (Fig. 1 and Fig. 2).

Discussion

This study revealed that silver would tend to subtly accumulate to a greater extent in the hair and blood of the depressed people for the reasons not yet well understood. The analyzed sample concentrations and reference values we reported for silver in the hair and blood in this study are close to those of Creason et al. (1975), Wan et al. (1991), Bermejo-Barrera et. al. (2002), and Toxiba, Switzerland (another trace element analyzing laboratory). Random quality control sampling of cadmium, copper, lead, molybdenum, and zinc in the blood and hair also showed a remarkable congruency of results obtained by the ICP-MS and differential pulsed anodic stripping voltammetry (DPASV) (Momčilović, Ivičić, 2003; Ivičić, Momčilović, 2003).

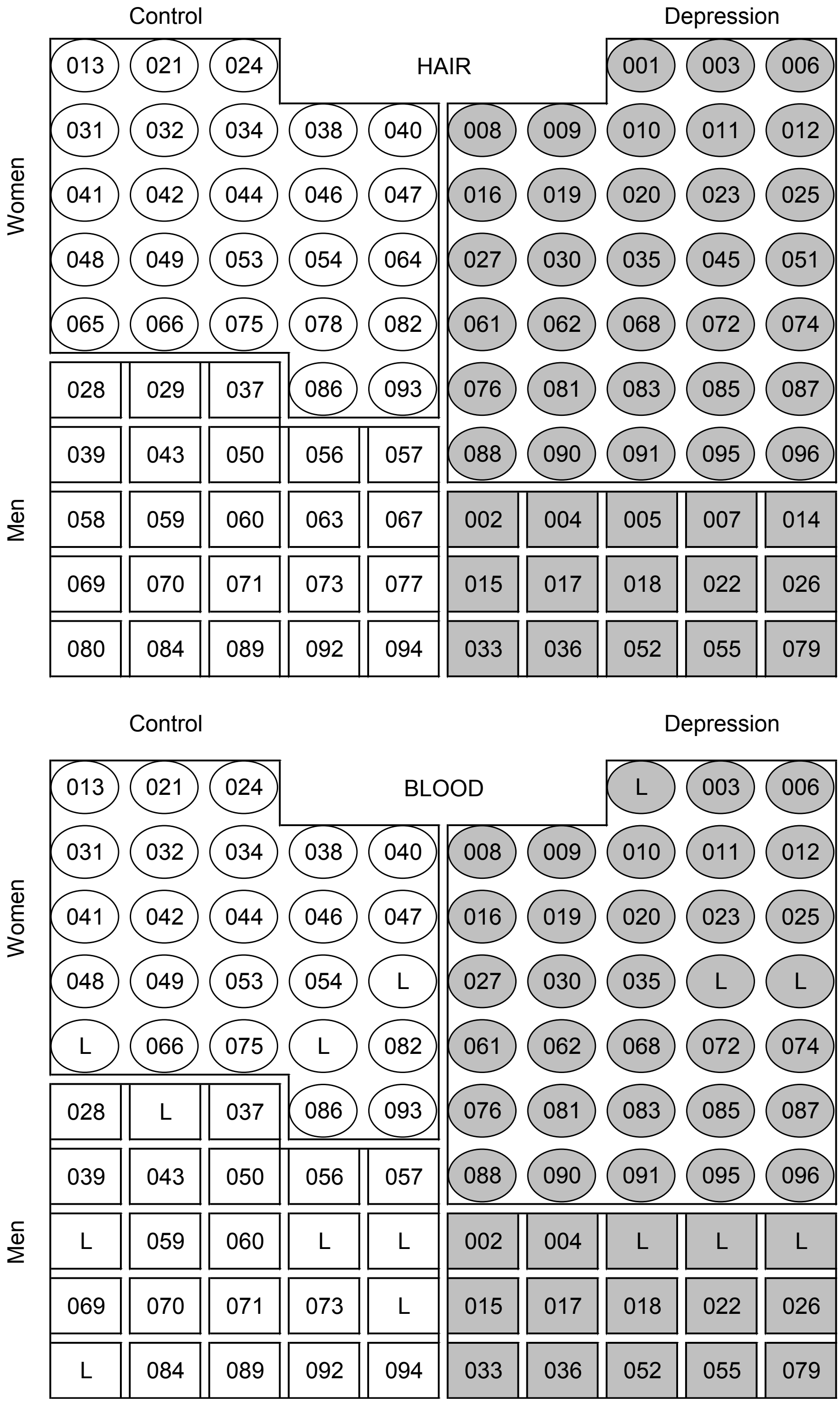
We observed about two orders of magnitude higher silver accumulation in the hair than in the blood. Silver has a very high affinity for sulfur so that sulfur or sulfur containing foods should never be served on silver or silver plated utensils (Emsley, 2001). Thus, it is not surprising that hair, rich in chondroitine sulphate (Rook, Dawber, 1982), tends to avidly accumulate silver to a much greater extent than it can be found in the blood.

The reason why silver tends to accumulate more in the hair and blood of depressed than control subjects remains to be elucidated. Since silver has a strong ant-

Table 2. Linear part of the rank sequence slope for silver in the hair and blood of control and depressed subjects (Insert to the Fig's 3 and 4, respectively).

	Hair	Blood
Control	$^{a}Y = (94.9\ X \pm 5.34)\ 10^{-5}$	$Y = (2.50\ X \pm 0.098)\ 10^{-5}$
Depressed	$^{b}Y = (244.0\ X \pm 6.97)\ 10^{-5}$	$Y = (4.54\ X \pm 0.397)\ 10^{-5}$

[a,b]Means (± standard error) bearing various superscripts in the same column differ significantly ($P < 0.01$)



Appendix.1. Code matrix data set for the collected hair and blood samples in the control and depressed subjects. ○ Control women, ● Depressed women, □ Control men, ■ Depressed men. The number of the subject is inserted in the corresponding circle of square (topological site) to allow for the cross-element comparison for every subject of this randomized double-blind prospective clinico-epidemiological investigation

CONTROL					(μg/g)	DEPRESSION				
Subject #	Sex	Age	Hair	Blood		Subject #	Sex	Age	Hair	Blood
071	1	54	0,010	0,000346		018	1	58	0,003	0,013300
075	0	57	0,010	<0,00006		076	0	21	0,006	<0,00006
073	1	56	0,011	0,000254		011	0	65	0,008	<0,0003
093	0	35	0,012	<0,00006		026	1	61	0,008	<0,0003
067	1	25	0,013	Lost		016	0	53	0,009	<0,0003
013	0	24	0,014	<0,0003		017	1	62	0,015	0,002000
084	1	52	0,014	<0,00006		095	0	70	0,015	<0,00006
021	0	60	0,015	0,002400		052	1	64	0,016	<0,00006
080	1	47	0,015	Lost		045	0	52	0,022	Lost
069	1	56	0,016	0,000077		012	0	56	0,024	<0,0003
029	1	66	0,018	Lost		022	1	50	0,024	0,000900
056	1	44	0,018	0,001611		007	1	62	0,031	Lost
059	1	37	0,018	0,000322		036	1	24	0,031	<0,00006
042	0	44	0,020	0,001076		015	1	48	0,035	<0,0003
077	1	59	0,020	Lost		072	0	47	0,036	0,000162
086	0	25	0,024	<0,00006		061	0	52	0,037	0,000130
089	1	72	0,024	<0,00006		033	1	44	0,040	0,000195
058	1	67	0,027	Lost		055	1	51	0,042	<0,00006
060	1	55	0,028	0,000150		020	0	59	0,046	0,010600
078	0	91	0,028	Lost		035	0	54	0,062	<0,00006
082	0	53	0,028	0,000302		006	0	49	0,065	0,005000
064	0	55	0,033	Lost		025	0	50	0,065	0,000300
066	0	51	0,036	0,000742		019	0	33	0,070	0,003600
070	1	53	0,036	0,000403		081	0	43	0,070	0,000490
053	0	36	0,040	0,000118		023	0	49	0,077	0,003300
094	1	40	0,040	<0,00006		091	0	22	0,077	0,000393
031	0	42	0,042	<0,00006		085	0	51	0,089	<0,00006
034	0	52	0,046	<0,00006		030	0	26	0,091	0,000416
039	1	34	0,046	0,000234		004	1	31	0,096	0,002900
028	1	50	0,048	0,000090		074	0	49	0,105	0,000060
037	1	63	0,060	0,000204		090	0	61	0,107	<0,00006
040	0	47	0,062	<0,00006		003	0	55	0,117	0,008500
032	0	58	0,064	0,000970		068	0	47	0,117	0,000206
057	1	50	0,064	0,000168		002	1	53	0,120	0,012100
043	1	44	0,074	<0,00006		001	0	51	0,136	Lost
063	1	63	0,088	Lost		008	0	63	0,148	<0,0003
046	0	45	0,090	<0,00006		051	0	58	0,153	Lost
024	0	40	0,099	0,000400		083	0	23	0,208	<0,00006
047	0	56	0,109	0,000167		005	1	26	0,222	Lost
041	0	25	0,110	<0,00006		027	0	43	0,230	0,003400
049	0	48	0,165	<0,00006		062	0	41	0,232	0,000153
092	1	58	0,170	<0,00006		087	0	50	0,256	<0,00006
054	0	57	0,176	0,000077		014	1	37	0,297	Lost
065	0	80	0,245	Lost		010	0	35	0,346	0,137700
048	0	49	0,708	<0,00006		009	0	28	0,358	0,169300
050	1	60	0,765	0,284004		079	1	53	0,531	<0,00006
044	0	53	1,170	<0,00006		088	0	44	0,779	<0,00006
038	0	56	1,190	0,000545		096	0	57	1,040	<0,00006

Appendix 2. Actual data set on silver concentration in the hair and whole blood of the control and depressed subjects (μg Ag/g tissue); 0 – Women, 1 – Men. Hair values are shown in the increasing order.

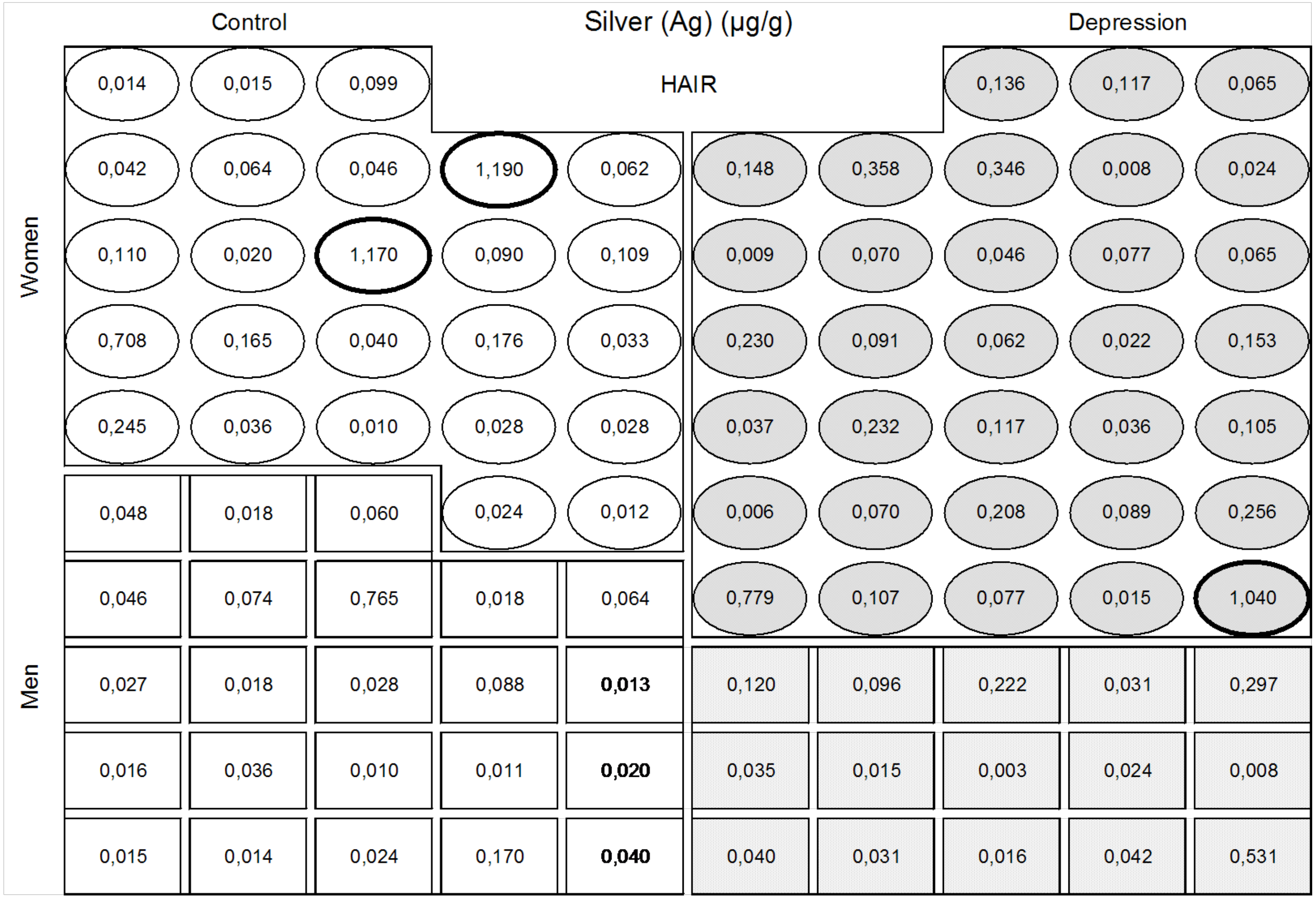


Fig.1. Silver in the hair of control and depressed subjects (μg Ag/g hair). ○ Control women; ● Depressed women; □ Control men; ■ Depressed men. Actual Ag concentration for every subject is shown within the appropriate circle or square; their margins are bolded if silver is above CBM reference values of 0.8000 μg/g. Note that every subject represents almost 1% (n = 96 = 100%) in this topological code matrix (see Appendix 1).

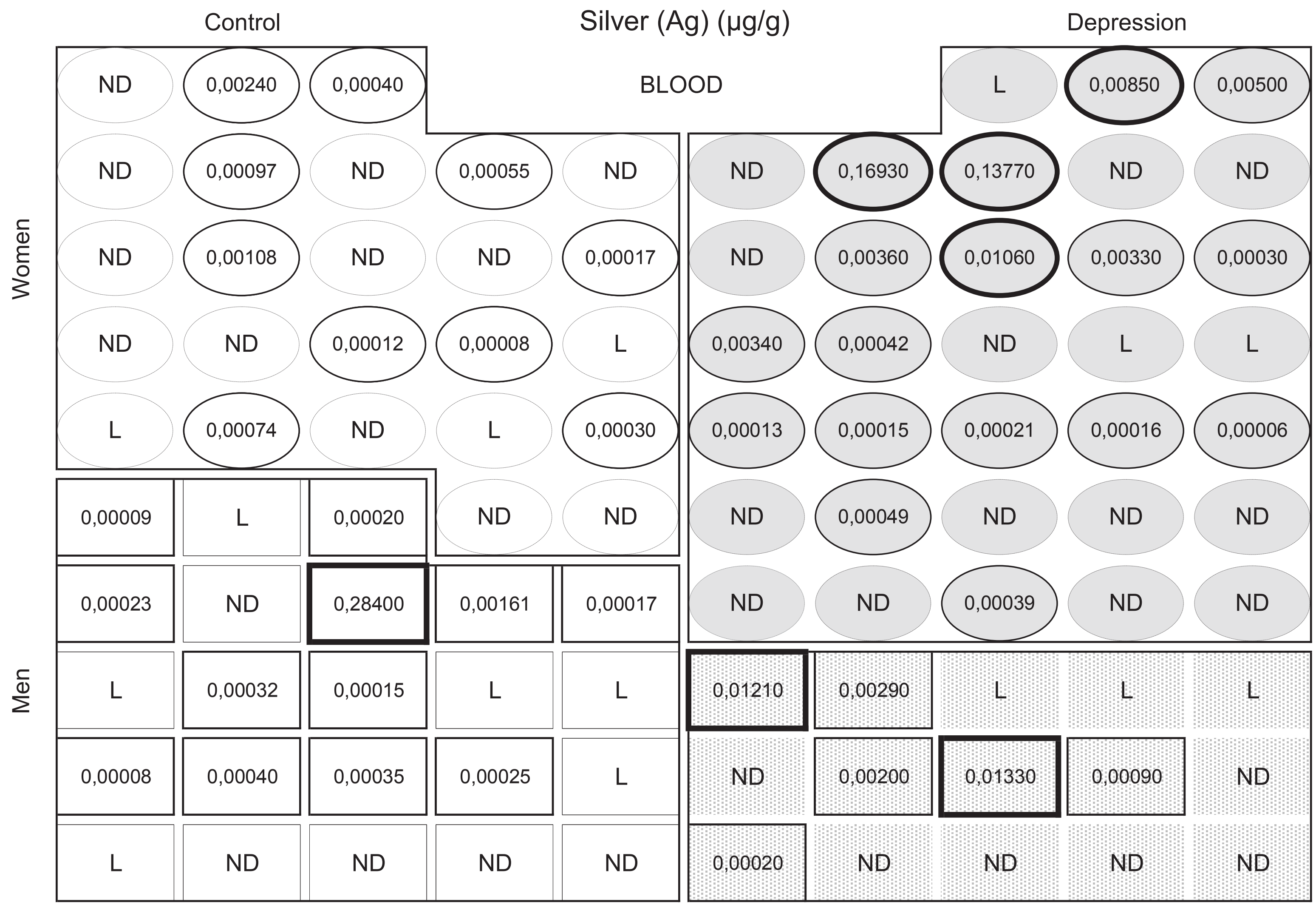


Fig. 2. Silver in the whole blood of control and depressed subjects (µg Ag/g whole blood). ○ Control women; ● Depressed women; □ Control men; ■ Depressed men; L sample lost; ND not detectable (some silver present but below the detection limits for accurate quantitative determination). Actual Ag concentration for every subject is shown within the appropriate sign; their margins are bolded if silver is above CBM reference values of 0.0005 µg/g. Note that every subject represents almost 1% (n = 96 = 100%) in this topological code matrix (see Appendix 1).

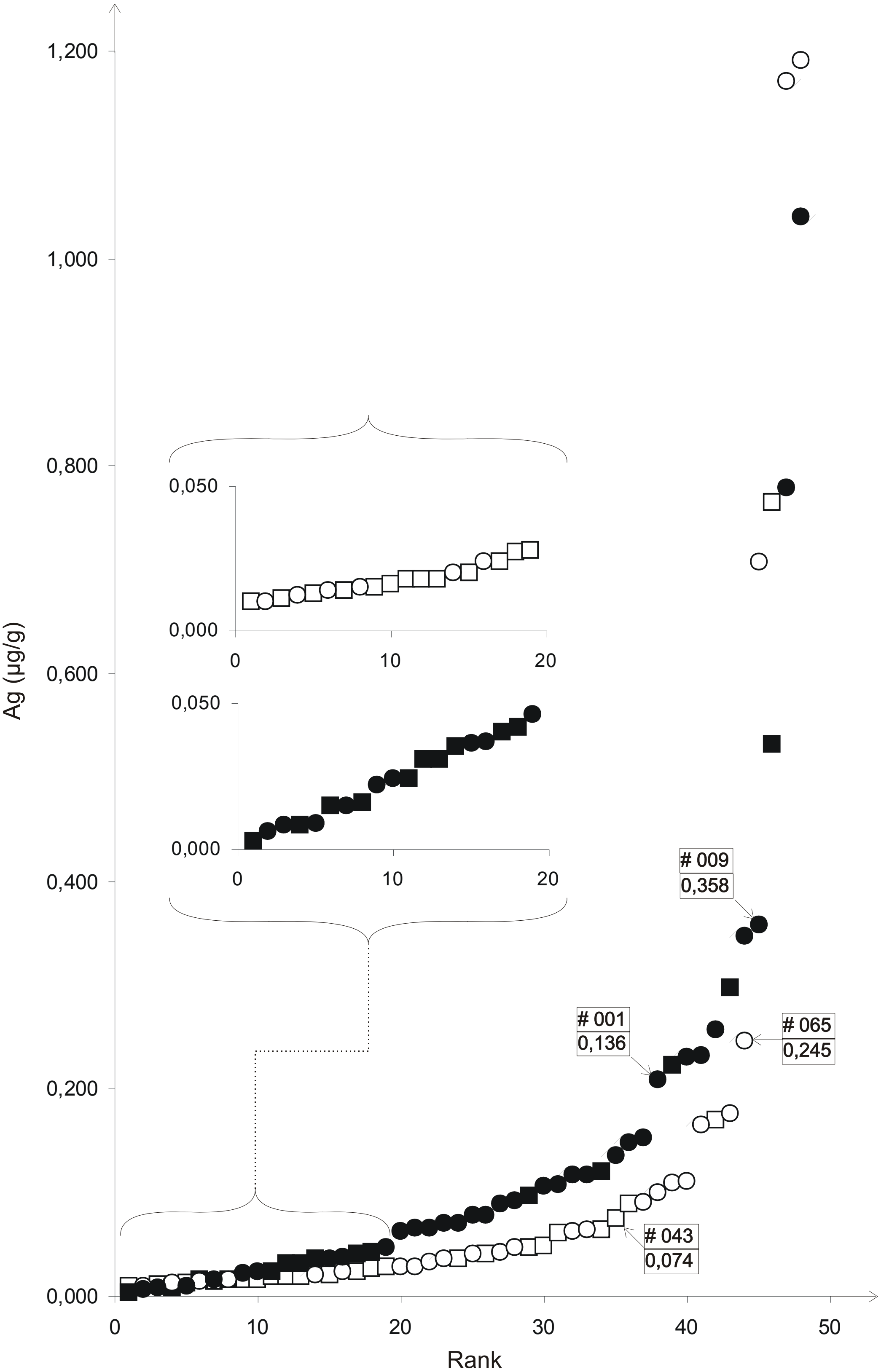


Fig.3. Rank sequence of silver in the hair (µg Ag/g hair) of control and depressed subjects (n = 96). ○ Control women, ● Depressed women, □ Control men, ■ Depressed men. The linear portion of the curve is shown in the insert. The deflection part of the curve, and the maximal values, are marked with the subject number and the actual concentration of silver measured within the box.

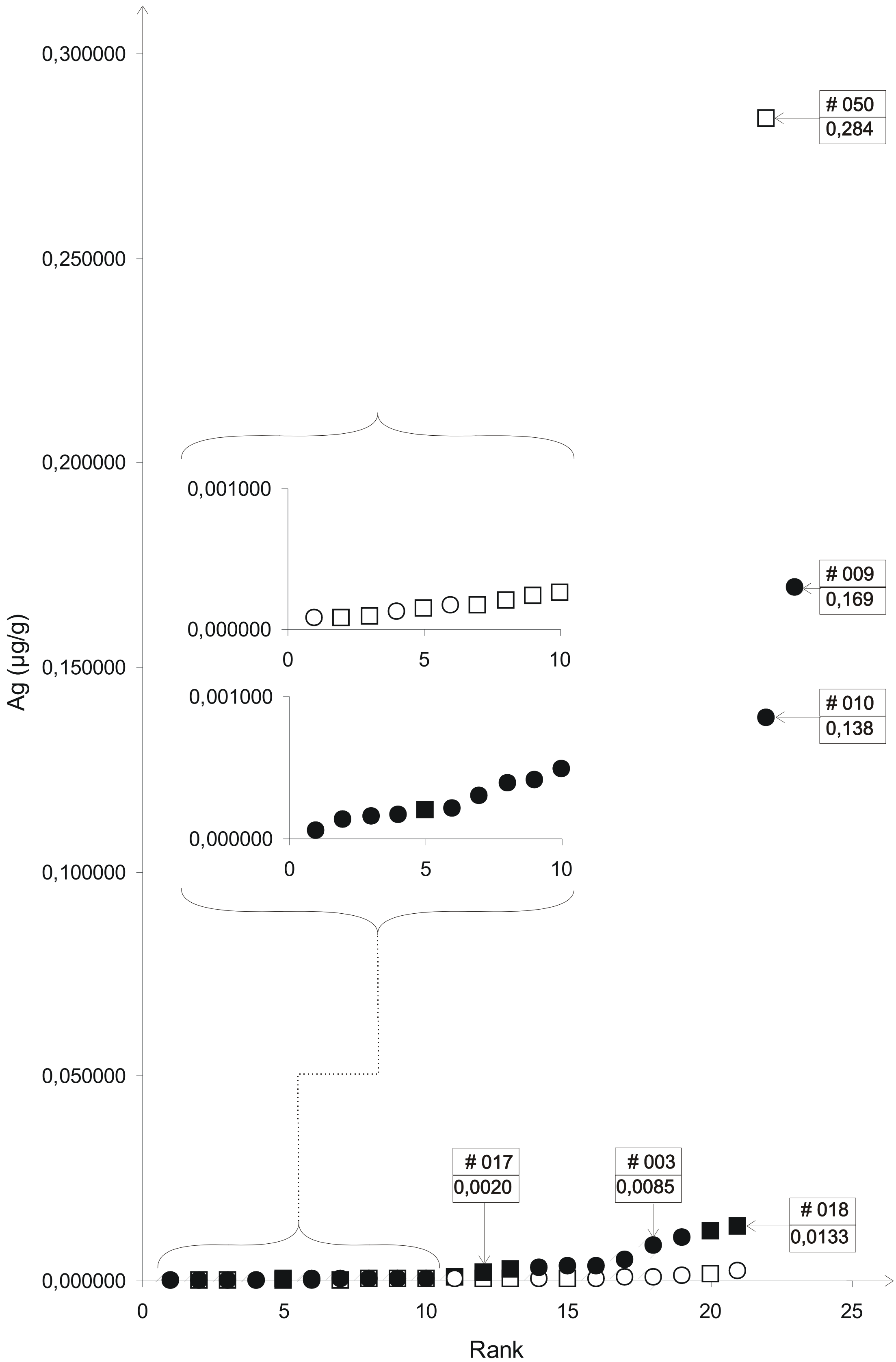


Fig.4. Rank sequence of silver in the whole blood (µg Ag/g whole blood) of control and depressed subjects (n = 45)..○ Control women, ● Depressed women, □ Control men, ■ Depressed men. The linear portion of the curve is shown in the insert. The deflection part of the curve, and the maximal values, are marked with the subject number and the actual concentration of silver measured within the box.

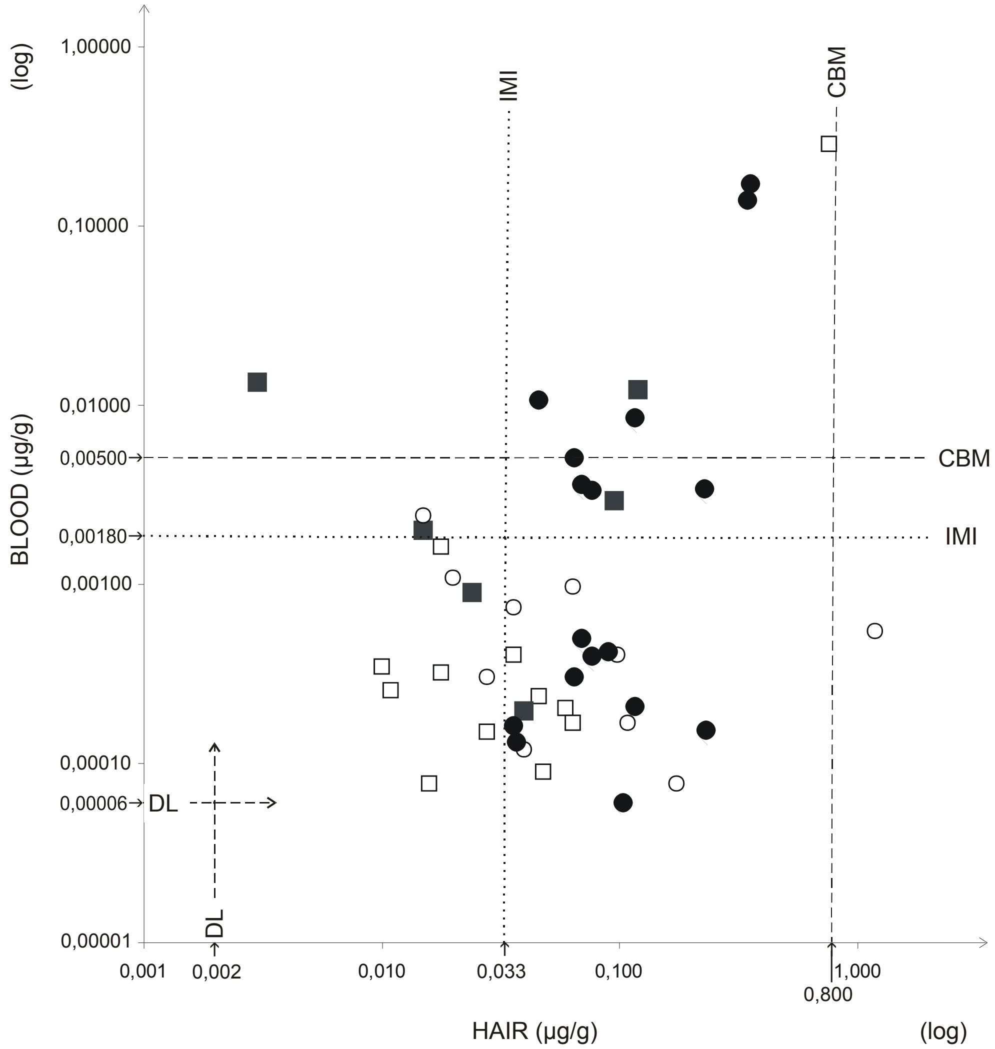


Fig.5. Cross-plot of silver in the hair versus silver in the whole blood of control and depressed subjects, respectively (µg Ag/g tissue). There were 45 subjects where both hair and blood silver samples were available for analysis). ○ Control women, ● Depressed women, □ Control men, ■ Depressed men. ----- CBM Center for Biotic Medicine, Moscow, reference values for Ag,; ····· IMI Institute for Medical Research and Occupational Health, Zagreb, suggested more stringent reference values for Ag; LD limits of quantitative detection.

Table 3. Frequency distribution of silver in the blood and hair for the matched samples of depressed and control subjects by IMI criteria (n = 45).

Element\Tissue	Blood[a]		Hair[b]	
Ag (µg/g)	< 0.0018	> 0.0018	< 0.033	> 0.033
Control	20	2	9	13
Depression	11	12	3	20

bactericidal activity (see Introduction), it is possible that the level of circulating bacteria may be higher in the depressed than the control subjects. Alternatively, the impaired liver may produce a somewhat miss-folded conformation of a protein similar to some hypothetic bacterial target protein or lipid with high affinity for silver, or having some hormone blocking or neurotransmitter signal processing qualities. Thus, in many aspects, the functional role of liver in the miss folded protein (lipo-protein, glyco-protein, glyco-lipid, glyco-lipo-protein) synthesis may be crucial for the development of depression and, perhaps, some other psychiatric diseases of unknown origin.

There is yet another important link associating silver with depression and that is interaction of silver with copper and selenium. Indeed, it has been shown that excess silver would aggravate both the copper deficiency and selenium deficiency (Underwood, 1977 a, b). Thus, Matsumura et al. (1992) reported high selective binding of silver to selenium. Hence, silver would behave antagonistically, like molybdenum, in relation to copper (Momčilović, 1999), and if both silver and molybdenum are increased, the copper may became deficient, or more deficient if already deficient. In our preliminary work (Momčilović et al., 2006a) we already reported the association of depression with lack of iodine, selenium, and copper. Surprisingly enough, no data is available about the possible adverse effect of silver upon the iodine and/or thyroid function and metabolism. Recently, it was reported that silver may inhibit excessive fibrocyte formation in the Grave's Disease (iThyroid.com). Our data on copper and selenium of the subjects involved in this study already in the process of analyzing and would be viewed in a new light considering the data on metabolic imaging of silver in depression (Momčilović et al., 2007 a,b).

It is intriguing to speculate that the so called fatalistic attitude attributed to the culturological specificity in some Asian people may in fact be a widespread sign of excess dietary silver exposure in the countries of the Islamic world (Tipton et al.,1965). Thus, Lal et al. (1989) found by neutron activation analysis of precleansed human scalp hair geometrical mean of 1.927 ± 1.1 μg/g silver in the Panjab population which compared with values of 0.39 ± 2.50 μg/g seen in other parts of India, or 0.16 ± 2.11 μg/g in Japan, where such dietary habits are not known to exist.

Conclusions

Simultaneously increased concentration of silver in the blood and hair is to be found more often in the depressed than the control subjects. Silver is preferentially accumulated in the hair than whole blood by almost two orders of magnitude.

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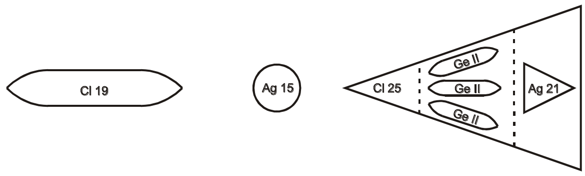

Vignette 2. Silver structure– Occult view.

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